

# PATENT SPECIFICATION

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## (54) TOBACCO AND TOBACCO-CONTAINING MANUFACTURES

(71) We, WILKINSON SWORD LIMITED, a British Company, of Sword House, High Wycombe, Buckinghamshire, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

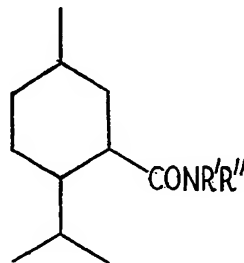
This invention relates to tobacco and tobacco-containing manufactures in which there is incorporated an ingredient capable of stimulating the cold receptors of the nervous system in the nasal and oral mucosa to give a "cool" sensation when the smoke is inhaled or when the tobacco itself is brought into contact with the nasal and/or oral mucosa.

It is well known to add to tobacco and tobacco-containing manufactures an amount of an ingredient which gives a "cool" sensation during smoking. Widely used for this purpose is menthol, and mentholated cigarettes and tobacco are sold on an extensive scale. However, the use of menthol for this purpose has its disadvantages, for example, the volatility of menthol means that the mentholated products, in particular, mentholated cigarettes tend to lose the "coolant" activity and thus lack storage stability. Also the characteristic minty odour of menthol can be disadvantageous in tobacco and tobacco-containing manufactures.

The present invention seeks to provide tobacco and tobacco-containing manufactures containing an ingredient which creates a "cool" sensation when the ingredient comes into contact with the nasal and/or oral mucosa, either in the tobacco smoke, or by direct contact of the tobacco on the nasal or oral mucosa, but which does not have the disadvantages of volatility and strong odour associated with menthol.

According to the present invention, we have discovered a group of compounds having a cooling effect on the nasal and oral mucosa but without the disadvantages of volatility and strong odour. These compounds are N-

substituted *p*-menthane carboxamides of the formula:



where

R', when taken separately, is hydrogen or an aliphatic radical containing up to 25 carbon atoms;

R'', when taken separately, is hydroxy, or an aliphatic radical containing up to 25 carbon atoms, with the proviso that when R' is hydrogen R'' may also be an aryl radical of up to 10 carbon atoms and selected from the group consisting of substituted phenyl, phenalkyl, substituted phenalkyl, naphthyl and substituted naphthyl; and

R' and R'', when taken together, represent a cyclic or heterocyclic group of up to 25 carbon atoms.

In the above definitions "aliphatic" is intended to include any straight-chained, branched-chained cyclic radical free of aromatic unsaturation, and thus embraces alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, hydroxyalkyl, acyloxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, acylaminoalkyl, carboxyalkyl and similar combinations. "Aryl" is intended to include any radical containing aromatic unsaturation and includes alkaryl, aralkyl and like combinations.

In accordance with the present invention, therefore, we provide tobacco and tobacco-containing manufactures in which there is incorporated, in an effective amount, an agent capable of stimulating the cold receptors of

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the nervous system of the nasal and oral mucosa when brought into contact therewith upon use of the manufacture, wherein said agent comprises one or more N-substituted p-menthane carboxamides as defined above.

The N-substituted-p-menthane-3-carboxamides used in this invention may be readily prepared by conventional methods, such as by the reaction of the corresponding acid chloride (obtained by reacting p-menthane-3-carboxylic acid with thionyl chloride) with the appropriate mono- or di-substituted amine. The reaction will usually be carried out in solution in the presence of a hydrogen chloride acceptor e.g. sodium hydroxide. The reaction proceeds smoothly at room temperature.

The compounds used in this invention exhibit both geometric and optical isomerisation and, depending on the starting materials and the methods used, the compounds used in this invention may be isomerically pure, i.e. consisting of one geometric or optical isomer, or they may be isomeric mixtures, both in the geometric and optical sense.

As is well known, the basic p-menthane structure is a chair-shaped molecule which can exist in cis or trans forms. Substitution of the carboxamide group into the 3-position gives rise to four configurational or geometric isomers depending upon whether the substitution is axially or equatorially into the cis or trans isomer, the four isomers being related as menthol is to neomenthol, isomenthol and neoisomenthol. In general it is found that in the compounds used in this invention the equatorially substituted carboxamides have the greater cooling effect than the axial compounds and are to be preferred.

Substitution of the carboxamide group in the 3-position of the p-menthane structure also gives rise to optical isomerism, each of the above-mentioned four geometric isomers existing in *d*, *l* and *dl* forms. The physiological cooling effect is found, in most cases, to be greater in the *l*-form than in *d*-form, and in

some cases substantially greater. The compounds derived from the *l* form of p-menthane-3-carboxylic acid are therefore preferred.

The cooling sensation created by the compounds used in the invention on the mucous membranes of the mouth and nose varies both in intensity and longevity from compound to compound.

When either R' and R'' is aliphatic the preferred values are C<sub>1</sub>—C<sub>3</sub> straight or branched chain alkyl, C<sub>1</sub>—C<sub>3</sub> straight or branched chain hydroxyalkyl or aminoalkyl and C<sub>1</sub>—C<sub>4</sub> acylated derivatives thereof, and —C<sub>n</sub>H<sub>2n</sub>COOR''' or —C<sub>2</sub>H<sub>2n</sub>COOR''', where —C<sub>n</sub>H<sub>2n</sub> is a straight or branched chain alkylene radical in which *n* is an integer of from 1—6 and R''' is hydrogen or a C<sub>1</sub>—C<sub>3</sub> alkyl or hydroxyalkyl group, preferably a C<sub>1</sub>—C<sub>4</sub> straight chain alkyl group.

In general the monosubstituted compounds, i.e. where R' is H, are preferred although disubstituted compounds where R' and R'' are both C<sub>1</sub>—C<sub>3</sub> alkyl also show a very pronounced cooling effect. Most preferred of all are compounds where R' is H and R'' is C<sub>1</sub>—C<sub>3</sub> alkyl, C<sub>1</sub>—C<sub>4</sub> hydroxyalkyl, or —CH<sub>2</sub>COOR''', where R''' is C<sub>1</sub>—C<sub>3</sub> alkyl.

Also usable in accordance with this invention are compounds where R' is H and R'' is hydroxy or substituted phenyl, e.g. alkylphenyl, hydroxyphenyl, alkoxyphenyl, or halophenyl, of up to 10 carbon atoms, phenalkyl or substituted phenalkyl e.g. benzyl, naphthyl or substituted naphthyl, and compounds where R' and R'' are joined to form a cyclic group. When so joined R' and R'' preferably represent an alkylene chain, optionally interrupted by oxygen, which together with the nitrogen atom to which R' and R'' are attached forms a 5- or 6-membered heterocyclic ring.

Compounds falling within the scope of the formula defined and of particular note are given in Table I.

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TABLE I

R'	R''	m.p. °C	b.p. °C.
H	—CH <sub>3</sub>	95—7°	
„	—C <sub>2</sub> H <sub>5</sub>	82.5—84.5°	
„	—C <sub>3</sub> H <sub>7</sub> (n)	65—7°	
„	—C <sub>3</sub> H <sub>7</sub> (iso)	94—6°	
„	—CH <sub>2</sub> CH <sub>2</sub> OH		160°/.1 mm.
„	—(CH <sub>2</sub> ) <sub>3</sub> OH		170°/.1 mm.
„	—CH <sub>2</sub> CH(OH)CH <sub>3</sub>		184°/.1 mm.
„	—C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> OH	123°	
„	—CH <sub>2</sub> COOC <sub>3</sub> H <sub>7</sub> (n)		170°/.1 mm.
„	—CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>		150°/.1 mm.
—CH <sub>3</sub>	—CH <sub>3</sub>		56—57°/0.01 mm.
—C <sub>2</sub> H <sub>5</sub>	—C <sub>2</sub> H <sub>5</sub>		78—80°/0.05 mm.

Alternative compounds of the formula in accordance with this invention are given in defined and shown to have a cooling effect Table II.

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TABLE II

R'	R''	m.p. °C.	b.p. °C.
H	—C <sub>4</sub> H <sub>9</sub> (n)	88—90°	
„	—C <sub>4</sub> H <sub>9</sub> (iso)	111—112°	
„	—C <sub>4</sub> H <sub>9</sub> (sec)	116—119°	
„	—C <sub>4</sub> H <sub>9</sub> (tert)	145—146°	
„	—CH <sub>2</sub> COOH		
—CH <sub>2</sub> CH <sub>2</sub> OH	—CH <sub>2</sub> CH <sub>2</sub> OH		
H	—OH	124—125°	
	—(CH <sub>2</sub> ) <sub>4</sub> —	54—56°	
	—(CH <sub>2</sub> ) <sub>5</sub> —		102—104°/.05 mm.
	—CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> —		101—103°/.05 mm.
	—CH <sub>2</sub> CH <sub>2</sub> NHCH <sub>2</sub> CH <sub>2</sub> —		
—H	—CH <sub>2</sub> Ph	106—107°	

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TABLE II (Continued)

R'	R''	m.p. °C.	b.p. °C.
—H	—CH <sub>2</sub> C≡CCH <sub>2</sub> OH		180°/.1 mm.
"	—CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>		
"	—CH(CH <sub>3</sub> )COOC <sub>2</sub> H <sub>5</sub>		160°/.1 mm.
"	—(CH <sub>2</sub> ) <sub>6</sub> OH		220°/.1 mm.
"	—CH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub> OH		190°/.1 mm.
"	—CH <sub>2</sub> CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>		152°/.1 mm.
"	—CH <sub>2</sub> COOCH <sub>3</sub>		130—140°/.1 mm.
"	—CH(CH <sub>3</sub> )CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>		164°/.1 mm.
"	—CH <sub>2</sub> OH	141—2°	
"	—CH <sub>2</sub> CH <sub>2</sub> OCOCH <sub>3</sub>		159—162°/.1 mm.
"	—C <sub>5</sub> H <sub>11</sub> (n)	80—82°	
"	—C <sub>6</sub> H <sub>4</sub> OMe(p)	177°	
"	—C <sub>6</sub> H <sub>4</sub> OH(p)		230°/.1 mm.

The preparation of the compounds described above is described in more detail in our copending Application No. 3928/71 (Serial No. 1351761), to which reference should be made.

In formulating the tobacco and tobacco-containing manufactures of this invention the active compound may be incorporated directly into the tobacco, for example, by impregnation of the tobacco with an alcoholic solution of the active ingredient, at a suitable stage of manufacture. However, in an alternative and preferred arrangement, the active ingredient may be incorporated into a tobacco smoke filter for use in a pipe or cigarette filter or as a filter tip for cigarettes. The latter, in particular, forms a particularly effective utilisation of the present invention, the active compound simply being impregnated in the wad of material forming the filter tip. This may be of any of the well known types of filter tip for cigarettes, e.g. a filter pad of cellulose acetate, paper, cotton, α-cellulose or asbestos fiber. Conveniently the filter tip is impregnated with an alcoholic solution of the active compound and then dried to deposit the active compound therein.

The amount of active compound to be incorporated into the tobacco or tobacco-containing manufacture in accordance with the invention will vary from compound to com-

pound depending on the activity thereof, i.e. the amount thereof which it is necessary to place in contact with the skin to produce a noticeable cooling effect, and will depend also on the mode of application thereof, i.e. whether the compound is impregnated in the tobacco itself, or in a filter tip or in any other accessory. However, the actual amount is not critical to this invention and will be readily determinable by the person skilled in the art by means of a few simple tests. As a matter of guidance, however, it may be mentioned that with the more active compounds, as little as 0.003 mg. deposited on the filter tip of a tipped cigarette is effective.

The invention is illustrated by the following Examples.

#### Example I.

##### Cigarette Tobacco

A proprietary brand of cigarette tobacco was sprayed with an ethanolic solution of N,N-dimethyl-p-menthane-3-carboxamide and was rolled into cigarettes each containing approximately 5.0 micrograms of active compound. Smoking the impregnated cigarettes produced a cool effect in the mouth characteristic of mentholated cigarettes but without any attendant odour other than that normally associated with tobacco.

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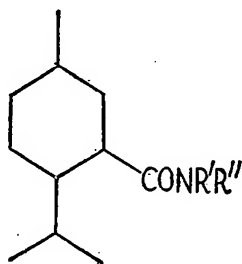
## Example II.

## Filter Tip Cigarettes

The filter tip of a proprietary brand of cigarette was impregnated with an ethanolic solution of N-ethyl-p-menthane-3-carboxamide in an amount sufficient to deposit in the filter 0.003 mg. of the active compound. Smoking the cigarette with the impregnated tip gave rise to a noticeable cooling effect in the mouth.

## WHAT WE CLAIM IS.—

1. A tobacco or tobacco-containing manufacture in which there is incorporated an agent capable of stimulating the cold receptors of the nervous system of the nasal and oral mucosa when brought into contact therewith upon use of the manufacture, wherein said agent is an N-substituted *p*-menthane carboxamide of the formula:



20 where

$R'$ , when taken separately, is hydrogen or an aliphatic radical containing up to 25 carbon atoms;

$R''$ , when taken separately, is hydroxy, or an aliphatic radical containing up to 25 carbon atoms, with the proviso that when  $R'$  is hydrogen  $R''$  may also be an aryl radical of up to 10 carbon atoms and selected from the group consisting of substituted phenyl, phenalkyl, substituted phenalkyl, naphthyl and substituted naphthyl; and

$R'$  and  $R''$ , when taken together, represent a cyclic or heterocyclic group of up to 25 carbon atoms.

2. A manufacture according to claim 1, wherein said N-substituted-*p*-menthane carboxamide is of the formula defined, where  $R'$ , when taken separately, is hydrogen,  $C_1-C_6$  straight or branched chain alkyl,  $C_1-C_6$  straight or branched chain hydroxyalkyl or aminoalkyl or a  $C_1-C_4$  acylated derivative thereof, or  $-C_nH_{2n}COR'''$  or



where  $-C_nH_{2n}$  is a straight or branched chain alkylene group in which  $n$  is an integer of from 1—6 and  $R'''$  is hydrogen or  $C_1-C_8$  alkyl or  $C_1-C_8$  hydroxyalkyl;  $R''$ , when taken separately, is an organic group as defined above for  $R'$ ,  $R'$  and  $R''$  being the same or different; and  $R'$  and  $R''$ , when taken together,

represent an alkylene chain optionally interrupted by oxygen and forming, together with the nitrogen atom to which  $R'$  and  $R''$  are attached, a 5- or 6-membered ring.

3. Manufactures according to claim 1, wherein said agent is of the formula defined where  $R'$  and  $R''$  are both alkyl of 1—3 carbon atoms.

4. Manufactures according to claim 1, wherein said agent is of the formula defined where  $R'$  is hydrogen and  $R''$  is alkyl of 1—3 carbon atoms, hydroxyalkyl of 1—4 carbon atoms or  $-CH_2COOR'''$ , where  $R'''$  is alkyl of 1—4 carbon atoms.

5. A manufacture according to claim 1, wherein said agent is one or more of the following:

N-methyl-*p*-menthane-3-carboxamide;

N-ethyl-*p*-menthane-3-carboxamide;

N-*t*-butyl-*p*-menthane-3-carboxamide;

N-*p*-menth-3-oylglycine ethyl ester;

N - (1,1 - dimethyl - 2 - hydroxy ethyl)-*p*-menthane-3-carboxamide;

N-*p*-menth-3-oylglycine *n*-propyl ester.

6. A manufacture according to any one of the preceding claims, which comprises tobacco impregnated with said agent.

7. A manufacture according to any one of claims 1—6 in the form of a cigarette into which is incorporated said agent.

8. A manufacture according to claim 7, in the form of a filter-tipped cigarette.

9. A manufacture according to claim 7 or 8, in which the agent is impregnated in the tobacco.

10. A manufacture according to claim 8, in which the agent is impregnated in the filter tip.

11. A tobacco smoke filter comprising a filter pad into which is incorporated one or more N-substituted-*p*-menthane carboxamides of the formula defined in claim 1.

12. A method of stimulating the cold receptors of the nervous system of the nasal and oral mucosa which comprises inhaling tobacco smoke in which there is entrained one or more N-substituted-*p*-menthane carboxamides of the formula defined in claim 1.

13. A method according to claim 12, wherein the tobacco smoke containing said carboxamide is produced by smoking a tobacco or tobacco-containing manufacture according to any one of claims 1—10.

14. A method according to claim 12, wherein the carboxamide is entrained in said smoke by passage of the smoke through a filter as claimed in claim 11.

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